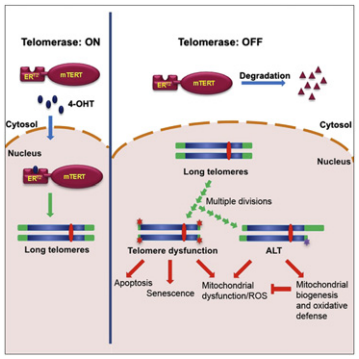
In This Issue

Cell



Control ALT, Delete Cancer

PAGE 651

Telomerase inhibition is an emerging therapeutic approach for numerous cancers. Here, Hu et al. demonstrate that inhibiting telomerase causes cell death in a mouse model of T cell lymphoma, but resistant cells eventually emerge as tumors acquire alternative lengthening of telomeres (ALT) and aberrant mitochondrial function. Surprisingly, these resistant cells are sensitive to PGC-1β blocking, offering a target for enhancing the effectiveness of antitelomerase therapy.

atTAKing Colon Cancer

PAGE 639

KRAS mutations in colon cancers define a generally chemorefractory subtype. *APC* mutations may cooperate with mutant *KRAS* to drive Wnt-signaling pathways. Singh et al. identified the TAK1 kinase as a key node that links KRAS to activated Wnt signaling in *APC*-deficient cancer cells. TAK1 inhibition leads to apoptotic cell death and tumor regression in KRAS-dependent colon cancers, making this kinase an attractive candidate therapeutic target for a treatment-refractory subset of colon cancers.

Polygamous Polycomb

PAGE 664

The Polycomb-repressive complexes have been thought to act hierarchically, with PRC2 catalyzing H3K27 methylation that, in turn, recruits PRC1 to catalyze H2A ubiquitylation. Tavares et al. now show that, although this pattern holds when the PRC complex includes the CBX subunit, an alternative PRC2 complex in which the RYBP protein replaces CBX allows for PRC1-mediated ubiquitylation independent of H3K27 methylation. This alternative complex is important for ES cell maintenance and X chromosome silencing and points to different varieties of PRCs carrying different functions.

Transcription Initiation in the Limelight

PAGE 679

Activator-dependent bacterial transcription shows many parallels to enhancer-dependent eukaryotic transcription. Using optical microscopy, Friedman and Gelles directly observe and quantitatively define the pathway of initiation at an activator-dependent bacterial promoter. The study identifies key constraints on and opportunities for transcription regulation at these promoters and presents an approach with broad applicability.

Elongation Factor for the PolyQ Long Haul

PAGE 690

Trinucleotide repeats encoding lengthy polyglutamine (polyQ) stretches occur in Huntington's disease and other inherited neurological disorders. Liu et al. find that the transcription elongation protein Spt4 is needed to transcribe elongated segments of trinucleotide repeats both in protein-coding and nonprotein-coding regions. Spt4 deficiency selectively reduces production and aggregation of mutant polyQ-containing proteins, revealing a potential target for the treatment of neurological disorders caused by expanded trinucleotide regions.

A Lipid Hotline to TORC

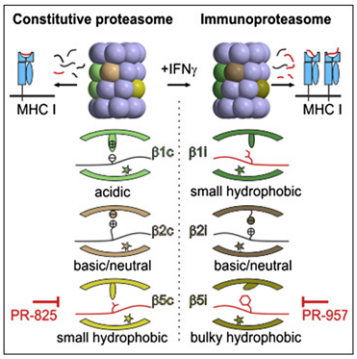
PAGE 702

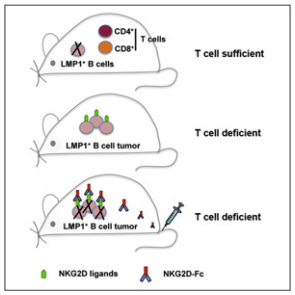
Using a combination of genetic, biochemical, and metabolomics approaches, Mousley et al. identify Kes1 as a mediator of membrane trafficking and lipid signaling that modulates nutrient sensing and cellular proliferation. The Kes1 pathway bridges nutrient transport at the plasma membrane to TORC1 signaling and Gcn4-driven transcriptional responses, providing an example of how oxysterol-binding proteins can serve as key mediators for spatially distinct cellular processes.

Inside the Immunoproteasome

PAGE 727

Immunoproteasomes generate peptides that differ from constitutive proteasomes, influencing antigen presentation and the immune response. Selective inhibition of the immunoproteasome is a promising treatment for autoimmune diseases. Huber et al. now provide structural insights into the molecular differences between the constitutive proteasome and the immunoproteasome and explain why the immunoproteasome is more competent in producing MHC-I ligands and why it is preferentially targeted by the inhibitor PR-957.





Harnessing Natural Killers to Fight B Cell Lymphoma

PAGE 739

In immunosuppressed patients, Epstein-Barr virus (EBV) frequently causes B cell lymphomas. Zhang et al. establish a mouse model for this disorder through the transgenic expression of a single EBV protein and use this model to develop a potential therapy based on tumor recognition by natural killer cells.

Modeling Mitochondrial Disease in Mice

PAGE 716

Raimundo et al. have used a transgenic approach to generate a mouse model of a deafness syndrome that is caused by a mitochondrial mutation in humans. Their studies reveal a tissue-specific apoptotic pathway triggered by mitochondrial stress and provide insight into the mechanism of maternally inherited deafness. This first mouse model of a mitochondrial disease will be valuable for addressing the complex tissue specificity of mitochondrial disease pathogenesis in general.

Axonal Mitochondria Welcome Unexpected Guest

PAGE 752

Using subcellular proteomics, Yoon et al. reveal that Lamin B2, an intermediate filament protein usually associated with the nuclear membrane, is synthesized in axons, localizes to mitochondria, and is critical for axon maintenance. This new function for Lamin B2 could provide insight into the cell type-specific nature of some laminopathies.

JAK Sets Circadian STATus

PAGE 765

How do circadian signals in the brain control whole-organism behavior? Luo and Sehgal provide insight into this question by identifying a microRNA-JAK/STAT circuit that drives normal rhythms of rest and activity in *Drosophila*. They show that central clock neurons project to a subset of neurons that secrete the cytokine-like protein Upd in a miR-279-dependent manner, tracing cellular and molecular connections from oscillations in the central clock to circadian behaviors.

The Cost of a Single Gene

PAGE 792

Although most genes in eukaryotic genomes are highly conserved, only a minority have been found to have a loss-of-function phenotype in genetic screens. Ramani et al. develop an assay to measure the fitness costs of losing individual gene functions over several generations. These population-level assays reveal that the majority of worm genes are required for wild-type growth, suggesting that genetic networks are not robust to mutation, as previously proposed.

Cdc42 Is Actin Up

PAGE 803

Cell polarity relies on the spatial assembly of signaling networks along the plasma membrane. Here, Orchard et al. take advantage of a simple bacterial infection paradigm to probe the molecular mechanisms underlying these processes. The *E. coli* protein Map, a bacterial guanine-nucleotide exchange factor, influences host cell polarity by establishing a connection with host cell F-actin to shape the timing and location of Cdc42 activity on the plasma membrane.

The Mammalian Methylome Base by Base

PAGE 816

What are the epigenetic differences between two haploid genomes inherited from each parent? Xie et al. generate a whole-genome, base-resolution map of allelic DNA methylation in the brain. They identified many loci that are differentially methylated, dependent on the parent of origin, including at noncanonical non-CG sites. They also discovered sequence signatures correlated with CG methylation that are evolutionarily conserved as well as previously unknown loci that are subject to imprinting, including miRNAs.

The Devil's Genome

PAGE 780

Tasmanian devil facial tumor disease (DFTD) is a transmissible cancer spread by biting that is threatening the Tasmanian devil with extinction. Murchison et al. have sequenced the genome of the Tasmanian devil as well as the genomes of two DFTD tumors. These sequences reveal that DFTD first originated in a female devil and has acquired somatic mutations, structural variants, and copy number alterations during its spread across Tasmania.